

# European Chemistry Congress

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## NMR molecular replacement, NMR<sup>2</sup>

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X-ray crystallography molecular replacement (MR) is a highly versatile tool for the detailed characterization of lead compounds and binding modes in the pharmaceutical industry. The two major limitations of its application to drug research are (i) the availability of a similar protein structure, which, in the area of structure-based drug design, is most often a complex of the protein with a lead compound, and (ii) obtaining well-diffracting crystals of the ligand-protein complexes of interest. While nowadays the first point is often not a limitation anymore, obtaining well-diffracting crystals might be difficult. In such situations structure determination of protein-ligand complexes by liquid-state NMR is a good option. Unfortunately, the established standard structure determination protocol is in general time-consuming, and a shortcut using available structural data as in the case of MR in X-ray crystallography is not available. Here, we present NMR<sup>2</sup>, a MR-like approach in NMR to determine the structures of the binding pockets of ligands at atomic resolution. The calculation of structures of protein-ligand complexes relies on the collection of unassigned semi-quantitative inter-molecular NOE distance restraints and on previously solved structures. The NMR<sup>2</sup> method uses a high throughput structure calculation protocol, rather than a docking-scoring simulation. It is fast since it requires only a few days of measuring time and bypasses the time-consuming sequential assignment steps for the protein. When applied to the cancer-relevant HDMX protein, the NMR<sup>2</sup> method yielded the structure of a ligand protein complex with an accuracy below 1 Ångstrom for the binding pocket irrespective of the starting protein structure templates used. We will present multiple NMR<sup>2</sup> applications covering a peptidomimetic inhibitor and small molecules that bind strongly or weakly to protein receptors. Our findings demonstrate that NMR<sup>2</sup> may open an avenue for the fast and robust determination of the binding pocket structure of ligand-protein complexes at atomic resolution without the need of diffracting crystals and high affinity ligands.

### Biography

Julien Orts has completed his joint PhD from the Max Planck Institute for Biophysical Chemistry in Göttingen & EMBL Heidelberg and Postdoctoral studies from ETH Zürich. He developed multidisciplinary approaches to study protein-small molecules complexes using NMR spectroscopy, X-ray crystallography and computational methods.

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